REMARKS

The present application is directed to methods for treating mammalian transplant tissue in such a manner as to temporarily ablate MHC Class I antigen complexes from the surface of the transplant tissue, thereby rendering the tissue suitable for transplantation into a host. After the transplanted donor tissue becomes established in the host (recipient), and after avoiding initial immune attack by killer T cells, the continuing expression of MHC Class I molecules and the returning presentation at the surface of MHC Class I antigen complexes, provides the normal mechanism for educating the host's immune system to identify the new (donor) tissue as "self" and to delete the population of natural killer T cells capable of recognizing and rejecting the donor tissue. The claims have been amended to emphasize the timely ablation of surface antigens and use of the donor tissue in transplantation before the reappearance of MHC Class I antigens on the donor tissue surface.

Applicant has amended Claims 1 and 12 to specifically recite that the donor tissues are viable and further to recite that the donor tissue is used prior to the reemergence of MHC Class I antigens on the surface of the tissue. Support for these amendments may be found throughout the specification and in particular at page 5, lines 14-18, and page 5, line 32 to page 6, line 12.

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Claim 15 (Group II) directed to treatment of donor tissue with papain, has been canceled and Claims 16, 17, 18, 19, 20, and 22 (formerly dependent on Claim 15) have been amended to depend from, and further define the subject matter of Group I, Claim 1 (Claim 22) and Group I, Claim 12, (Claims 16, 17, 18, 19, and 20). As such, Claims 16, 17, 18, 19, 20, 21 (dependent from Claim 20), 22, and 23, all formerly Group II, are now properly included within the subject matter of the claims of Group I. Support for these amendments may be found in the claims as originally filed.

No new matter has been added by the above-described claim amendments. The cancellation of any subject matter by the foregoing amendments is solely for the purpose of conforming the application to the restriction requirement made final in this Office Action or to clarify the patentable features of Applicant's invention. The foregoing amendments do not evidence any intention to abandon original inventive subject matter disclosured by Applicant, and Applicant reserves the right to prosecute any canceled subject matter in a subsequent application claiming priority to the present application.

35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 1-14 under 35 U.S.C. §112, second paragraph, stating that the phrase, "temporarily ablating MHC Class I antigens" as recited in Claims 1 and 12 is not properly defined in that no period of time constituting "temporarily" is provided in the specification other than the donor tissue being "temporarily" resistant to attack by the host's immune system.

In addition, the Examiner states that the recitation, "a period of time sufficient for MHC class I antigens to regenerate" in Claim 12 is indefinite as it is deemed to be unclear what period of time is "sufficient" for regeneration and further it is unclear when the second transplanting step takes place.

As stated above, the present application is directed to a method for inhibiting rejection of transplant tissue by treating the donor tissue with an enzyme to temporarily remove MHC Class I surface molecules which the host organism would initially recognize as foreign, resulting in rejection of the implanted tissue. It is important to note that the disclosed method does not alter, interfere, or inhibit the normal transcription and/or translation of the MHC Class I genes. According to the present specification,

> "Since the tissues will remain viable after treatment according to this invention, expression of MHC molecules will continue, and eventually reappearance of MHC antigens on the donor tissue will occur, e.g., after transplantation . . ." (See, sentence bridging pages 5 and 6).

Therefore, the temporary removal of the MHC Class I antigens creates a "window of opportunity" whereby the host's immune system does not recognize the implanted tissue as foreign and, according to the specification, as the MHC molecules gradually reappear on the surface after transplantation, the host's immune system is "re-educated" and will "accept" the newly expressed MHC antigens as "self" proteins. As stated in the disclosure,

> "Reappearance of MHC antigens may be used to advantage for inducing tolerance of the donor graft, through re-education of the recipient's immune system to recognize and tolerate the donor antigens as they reappear." (See, page 6, lines 6-8).

Therefore, "temporary ablation" or, in other words, the eventual reappearance of MHC Class I surface proteins is not (appreciably) under the control of the practitioner but rather is a function of natural cellular processes, which, as stated above, are not affected by the method of the present application. The claims have been amended to clarify that the re-emergence of MHC

Class I antigens is inherent in the continued viability of the transplant tissue and that the only timing that the practitioner must be concerned with is that the treated, viable donor tissue should be used prior to the reappearance of MHC Class I surface antigens on the surface of the donor tissue. Knowledge of the exact amount of time the donor tissue takes in re-establishing normal surface expression is not necessary to practice the invention.

Similarly, the term "a period of time sufficient for MHC Class I antigens to regenerate" is a reference to natural cellular processes which, again, are not affected by the method of the present application but is a function of normal, uninterrupted intracellular processes. The reference to this time period, which is largely out of the control of the practitioner, has been eliminated from the claims.

As disclosed in the specification, the second donor transplant referred to by the Examiner takes place after the recipient has developed a tolerance to the first donor tissue transplant,

> "Serial grafts from the same donor are contemplated for 'pre-tolerization' of a recipient, e.g., by first infusing syngeneic or isogeneic donor lymphocytes or other tissues treated according to this invention, which regenerate donor MHC antigens that are exposed to the recipient's immune system, after which a secondary transplant of donor tissue (treated or untreated) can be made to a recipient that is now tolerant of the donor graft." (See, page 6, lines 8-12).

In view of the amendments herein and the foregoing remarks, the rejections set forth under 35 U.S.C. §112, second paragraph, have been avoided or overcome. Withdrawal of the rejections are therefore respectfully solicited.

35 U.S.C. §102

The Examiner has rejected Claims 1-3 and 5-8 under 35 U.S.C. §102 as being anticipated by Oliver et al., U.S. Pat. No. 4,399,123 ("the '123 patent"). With respect to the '123 patent, the Examiner states,

> "The ['123 patent] is considered to anticipate the claimed invention because it teaches identical method for inhibiting transplant rejection comprising identical active steps of treating and transplanting donor tissues and identical structural elements including two enzymatic treatments and various combinations of donor tissues and host organisms as the claimed method." (See, Office Action at page 5).

Oliver et al. report a method for treating fibrous tissue first with a proteolytic enzyme such as trypsin to remove antigenic nonfibrous tissue proteins, followed by treatment of the tissue with a carbohydrate-splitting enzyme to remove polysaccharides, mucopolysaccharides and glycoproteins, which may or may not be antigenic (see, col. 3, lines 8-29), followed by treatment of the tissue with a stabilizer cross-linking agent such as glutaraldehyde. (See, e.g., col. 4, lines 38-48).

Applicant respectfully disagrees with the Examiner's assertion that the '123 patent teaches an identical method for inhibiting transplant rejection as the present application. There are in fact significant differences between the two disclosures. First, and most importantly, the treatment disclosed in the '123 patent results in the grafting of dead fibrous tissue. In contrast, the disclosure of the present application teaches a method for inhibiting transplant rejection by implanting live donor tissue in a recipient. The Examiner's attention is directed to Examples 1, 2, 3, 4, and 6 of the '123 patent. As is disclosed in all these examples, the initial tissue enzyme treatment (e.g., trypsin), includes incubation with sodium azide for 28 days. (See, for example, col. 6, lines 46-50). Applicant asserts that it is well known in the art that sodium azide is lethal to all eukaryotic cells and, as such, the treatment of tissue for 28 days with this chemical would most assuredly result in the death of all the cells of the tissue sample. As such, reassertion of any of the surface molecules normally present on the fibrotic tissue would be impossible.

In addition, as seen in Examples 1, 2, 3, 4, and 6 of the '123 patent, the fibrotic tissue treatment includes a glutaraldehyde crosslinking step, which, according to the '123 patent, and as discussed below, is essential if the grafted tissue is intended to be permanent. However, as with sodium azide, Applicant asserts that glutaraldehyde is also well known in the art to be lethal to all eukaryotic cells.

In addition, incubation with glutaraldehyde in the method of the present application would result in rejection of the donor tissue by the host organism. Treatment of the donor tissue according to the present invention leaves the majority of surface proteins intact. Crosslinking these proteins according to the prior art, whether with glutaraldehyde or polyisocyanates (as taught in the Oliver et al. '353 patent, also of record) would alter their natural structure; and the surface proteins that the donor and host have in common, i.e., which would not be recognized by the host as foreign, would in their crosslinked form appear foreign and result in an immune response and rejection of the donor tissue by the host.

Another significant difference between the present application and the '123 patent is that the '123 patent seeks to take advantage of the "natural" qualities of fibrotic tissue, i.e., strength,

flexibility, structure, and appearance, to provide a sterile, non-synthetic matrix for repair of tissue-related injuries:

> "According to one aspect of the present invention, there is provided a fibrous tissue preparation . . . which is suitable for heterotransplantation as a temporary dressing for cutaneous wounds and soft tissue injuries . . . " (See, col. 2, lines 9-13). (emphasis added).
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> According to another aspect of the present invention, there is provided a substantially nonantigenic fibrous tissue preparation . . . which is suitable for heterotransplantation as a permanent repair for cutaneous wounds and soft tissue injuries . . ." (See, col. 2, lines 17-21). (emphasis added).

As stated above, according to the '123 patent, fibrotic tissue possesses certain natural qualities that make it useful for grafting. For example, according to the '123 patent,

> "The purification procedure does not significantly affect the mechanical strength of the fibrous tissue and hence the utility of the purified fibrous tissue for the repair of injuries is not impaired." (See, col. 1, lines 63-66). (emphasis added).
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> "We have found that above 20°C the treatment results in an alteration of the fibre structure leading to a lower physical strength." (See, col. 2, lines 64-66). (emphasis added).
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> * * *
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> "We have also found unexpectedly that implanted purified fibrous tissue will inhibit the contraction of full thickness skin wounds which otherwise causes areas of distortion around the wound." (See, col. 5, lines 43-47).

In addition, according to the '123 patent, the advantage of fibrous tissue is its "skin-like" appearance:

> "In cutaneous wounds the implanted purified fibrous tissue becomes overgrown with epidermis provided it is covered by a suitable dressing and *eventually assumes the appearance of normal skin.*" (See, col. 5, lines 40-43). (emphasis added).

However, as seen from the disclosure, the fibrotic tissue of the '123 patent undergoes a harsh regimen of treatment with several enzymes and chemicals that strip all surface molecules, both antigenic and non-antigenic, and destroys all structures associated with the tissue viabililty, in order to produce a wound dressing that will be essentially inert in the host:

> "We have now found that the fibrous tissue of human or animal origin which is derived from dermis . . . can be purified so that all cellular elements such as sweat glands, sebaceous glands and vascular tissue are removed . . ." (See, col. 1, lines 56-62). (emphasis added).

and further,

> "While within a species such carbohydrate material may not be significantly antigenic, nevertheless it *does not contribute to the strength of the tissue* and may severely obstruct the subsequent recolonization of the graft by host cells such as fibroblasts and interfere with the formation of new capillaries within the graft." (See, col. 3, lines 12-18). (emphasis added).

As pointed out above, the advantage of the fibrous tissue for wound repair according to the '123 patent is the retention of a matrix structure and strength after harsh enzyme and chemical treatments and, as such, its structure provides a "skeleton-" or "scaffold-like" matrix which supports host cellular growth to facilitate repair at the site of the graft, without the requirement of any retained cellular functions associated with the once viable graft tissue itself:

> "This fibrous tissue preparation is capable of being infiltrated and colonized by the host cells of another individual . . . revascularized and, in some cases reepidermilized to form a permanent repair." (See, col. 2, lines 24-29). (emphasis added).
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> * * *
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> "In cutaneous wounds the implanted purified fibrous tissue becomes overgrown with epidermis provided it is covered by a suitable dressing and eventually assumes the appearance of normal skin." (See, col. 5, lines 40).

The Examiner also states, with respect to the '123 patent,

> "Moreover, [the '123 patent] teaches that after transplantation into the host mammal of the enzyme treated donor tissue there were no evidence of lymphocytes infiltration . . . and, thus, the treated transplant tissue was, at least 'temporarily', rendered resistant to immune-mediated attack by the host's immune system within the scope of the presently claimed invention." (See, Office Action, page 6).

The object of the present invention is not to temporarily avoid immune attack of donor tissue, but rather to treat donor tissue so that it will be tolerated by the host after transplant, even though it originated as non-endogenous tissue and even though it is transplanted as viable non-endogenous tissue. The fact that the present invention calls for the use of viable tissue is sufficient to distinguish it from the '123 patent, which, as demonstrated above, has the object of absolutely removing all viability from the structural fibrous implants that result from its teaching.

Therefore, unlike the treatment taught in the present application, the '123 patent describes the harsh (lethal) treatment of fibrotic tissue to remove or crosslink all surface molecules, remove structures associated with the tissue, for example, sebaceous glands, and sterilize the tissue, all in order to take advantage of its inert "fibrous" characteristics.

The '123 patent does not disclose or suggest the temporary removal of MHC Class I surface proteins specifically from viable mammalian donor tissue to facilitate successful transplantation of the live tissue to a recipient. Accordingly, the '123 patent is insufficient to anticipate any of the pending claims under 35 U.S.C. §102.

In the Office Action, the Examiner has rejected Claims 1-3, 5-7, 9, and 12 under 35 U.S.C. §102 as being anticipated by Oliver et al., U.S. Pat. No. 5,397,353 ("the '353 patent").

With respect to the '353 patent the Examiner states,

> "The ['353 patent] is considered to anticipate the claimed invention because it teaches an identical method for inhibiting transplant rejection comprising identical active steps of papain enzymatic treatment of donor tissues and two steps of transplanting." (See, Office Action at page 7).

Applicant asserts that the teaching of the '353 patent, like the '123 patent, is not related to a treatment for the temporary ablation of MHC Class I antigens on the surface of donor tissue for transplantation to a mammalian host and therefore, in contrast to the Examiner's assertion, does not teach an identical method for inhibiting transplant rejection. Similarly to the '123 patent, the '353 patent (having the same inventors as the '123 patent) also teaches a treatment that leads to the transplantation of dead fibrotic tissue. As seen in the '353 patent working examples, the fibrotic tissue undergoes a similarly harsh chemical treatment that includes a (lethal) 28-day incubation in sodium azide, followed by a nine-hour incubation in hexane diisocyanate as a crosslinking agent. Therefore, the tissue treatment disclosed in the '353 patent, i.e., involving sodium azide and crosslinking agents, would have the same detrimental effect on the donor tissue as discussed above in relation to the teaching of the '123 patent.

As in the '123 patent, the purpose of the method of the '353 patent is to strip virtually all viability from the tissue and to destroy virtually all the cellular elements associated with the dermal fibrotic tissue prior to implantation:

> "In accordance with one aspect of the present invention there is provided a substantially non-antigenic fibrous tissue preparation . . . which preparation is substantially free of non-fibrous tissue proteins and glycoproteins, is non-cytotoxic, substantially free of cellular elements, and substantially free of lipids and lipid residues . . . Those substances said to be '*substantially free*' of materials generally contain less than 5% of and preferably less than 1% of said materials." (See, col. 3, lines 15-42). (emphasis added).

Also, like the '123 patent, the '353 patent seeks to take advantage of the natural appearance and structural characteristics of fibrotic tissue that make it useful as a growth substrate for host cells:

> "It is a further advantage that in this process the original architecture of the collagenous fibrous material is preserved. The material is neither solubilized or denatured in the process so it natural structure is maintained which makes an implant derived from the material feel natural . . ." (See, col. 3, lines 7-12). (emphasis added).
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> "When implanted subcutaneously the new collagenous sheet material became recolonized by host cells and revascularized . . . Furthermore, in tissue culture the new material was found to become covered with a structural epidermis . . . and when implanted into skin wounds it became overgrown with epidermis and eventually appeared as normal skin apart from the *absence of hairs*." (See, col. 5, lines 10-22). (emphasis added).

Therefore, as with the '123 patent, the '353 patent teaches the grafting of dead (note the mention of the absence of hair, i.e., no protein expressed by the grafted tissue), sterile, fibrous tissue to take advantage of the structural or "architectural" characteristics that remain after harsh enzyme and chemical treatment.

In fact, not only does the '353 patent seek to take advantage of the structural characteristics of sterilized and completely denuded fibrotic tissue, Claim 1 specifically recites the characteristics retained by the treated tissue as well as the elements that have been stripped away, i.e., Claim 1 describes a structurally intact, dead fibrotic tissue,

> "1. A non-resorbable, substantially non-antigenic collagenous fibrous tissue preparation of human or animal tissue origin, which is suitable for homo- or heterotransplantation as a permanent repair for cutaneous wounds and soft tissue injuries, which preparation retains the natural structure and original architecture of said human or animal tissue, is substantially free of non-fibrous tissue proteins and glycoproteins, is substantially free of cellular elements, is substantially free of lipids and lipid residues and is non-cytotoxic, wherein said preparation is capable when implanted of being recolonized by host cells and revascularized while being resistant to calcification." (See, col. 7, line 24 to col. 8, line 9). (emphasis added).

Therefore, as stated above for the '123 patent, the '353 patent does not teach or suggest, and in no way communicates to the skilled practitioner, a treatment for viable tissue calling for temporary ablation of MHC Class I antigens from the surface of donor tissue *which leaves the ability of the tissue to regenerate MHC Class I antigens intact.* As with the '123 patent, the treatment disclosed in the '353 patent results in the permanent removal of all surface proteins from donor tissue which is no longer viable and, as such, would be unsuitable for practicing the novel method disclosed in the present application.

In addition, with reference to the '353 patent, the Examiner concludes,

> "Thus, the method for inhibiting transplant rejection of [the '353 patent] results in ablating, at least temporarily, of the immune-mediated attack by the host's immune system within the scope of the presently claimed invention." (See, Office Action, page 7).

Again, this is similar to the Examiner's assertion made relating to the teaching of the '123 patent. As stated above, the present invention is not related to temporarily "ablating" the immune-mediated attack of donor tissue; rather, the present invention seeks the permanent tolerance of donor tissue by a host via the method of (1) temporarily ablating (i.e, removing) surface molecules from the donor tissue that would otherwise signal the immune system to attack the donor tissue, while (2) retaining the viabililty of the donor tissue that would lead to subsequent re-establishment of such surface molecules and contribute to re-education of the host's immune system *in situ* to tolerate the non-endogenous donor tissue.

These concepts are absent from the '353 patent, and accordingly the rejection under 35 U.S.C. §102 based on the '353 patent should be withdrawn.

35 U.S.C. §103

The Examiner has rejected Claims 1-9 and 12-14 under 35 U.S.C. §103 as being unpatentable over Oliver et al., U.S. Pat. No. 4,399,123 and Oliver et al., U.S. Pat. No. 5,397,353 taken with Galati et al., *Cytometry*, 27: 77-83 (1997).

For the reasons set forth above, the teachings of the '123 patent and the '353 patent are unrelated to the novel methods taught in the present application.

With respect to Galati et al., the Examiner states,

> [Galati et al.] clearly particularly demonstrates that papain removes MHC Class I molecules of glycoprotein nature from cell surface (abstract) and it teaches that the MHC class I glycoproteins are expressed on nearly all nucleated cells . . . It also teaches that other than the MHC class I surface associated molecules remain unaffected by papain digestion . . ." (See, Office Action, paragraph bridging pages 9-10).

Applicant asserts that the Galati et al. reference, when considered either alone or in combination with the '123 and/or '353 patents, neither discloses nor suggests the invention disclosed in the present application. Galati et al. report a method for quantitating MHC Class I expression by flow cytometry. Essentially, Galati et al. sought an alternative to quantitating membrane molecules by the traditional method of analyzing surface-bound antibodies by employing "a combined cytometric/HPLC procedure" (see pg. 81, col. 2). According to this reference,

> "We relied on the well-described property of the enzyme papain to cleave the extracellular hydrophilic portion of MHC complexes from crude membrane preparations . . . We speculated that papain digestion of living cells could result in a quantitative decrease of the MHC-associated membrane fluorescence . . . Our speculation indeed proved correct, and soluble MHC molecules could easily be quantitated by HPLC analysis . . ." (See, Galati et al. at page 81, col. 2, to page 82, col. 1).

Therefore, Galati et al. report that MHC molecules can be quantitated after treatment of a crude cell extract with the enzyme papain. Galati et al. do not disclose or suggest treating mammalian donor tissue to temporarily remove MHC Class I surface antigen complexes to improve survival of transplanted donor tissue in a host organism. No mention of transplantation is made by Galati et al.

The combination of the '123 or '353 patents and Galati et al. do not suggest a method for inhibiting transplant rejection by treating viable donor tissue to temporarily ablate MHC Class I surface antigens and then transplanting the treated, viable tissue into a host. Accordingly, the combination of the '123 or '353 patents and Galati et al. is insufficient to render the present claims obvious within the meaning of 35 U.S.C. §103. Reconsideration and withdrawal of the rejection are respectfully requested.

In the Office Action, the Examiner has rejected Claims 10 and 11 under 35 U.S.C. §103 as being unpatentable over Oliver et al., U.S. Pat. No. 4,399,123 and Oliver et al., U.S. Pat. No. 5,397,353 taken with Galati et al., *supra*, all as applied to Claims 1-9 and 12-14 as stated above, further in view of Stone et al., *Transplantation*, 65: 1577-1583 (1998).

For the same reasons set forth above, the '123 and '353 patents, and the Galati et al. reference, considered in combination with Stone et al., do not teach or suggest the invention disclosed in the present application for inhibiting rejection of transplant tissue by temporarily ablating MHC Class I antigens from the surface of donor tissue prior to transplantation.

With respect to Stone et al., the Examiner states,

> "Stone et al. . . . discloses a method for inhibiting transplant wherein the method comprises step of treating donor tissue with galactosidase and step of transplanting the treated tissue in to host recipient and wherein the method results in a reduction of inflammatory reaction or immune response of recipient host." (See, Office Action, paragraph bridging pages 11-12).

Stone et al. report on the effect of eliminating α-gal epitopes from porcine meniscus and articular cartilage by incubation with α-galactosidase followed by implantation into the suprapatellar pouch of cynomolgus monkeys and monitoring of the immune response. (See, Stone et al., page 1578, right column, 1st paragraph).

According to Stone et al.,

> "This study shows that treatment of cartilage with α-galactosidase can successfully prevent anti-Gal immune response against the xenograft. However, the primate immune system reacts against cartilage-specific antigens, resulting in antibody formation as well as macrophage-mediated chronic inflammatory reaction in some of the xenografts." (See, page 1578, right column, 1st paragraph).

Stone et al. conclude,

> "Overall, the present study indicates that the enzymatic removal of α-gal epitopes from cartilage xenograft is an important first step in decreasing the immune rejection in primates." (See, page 1583, left column, last paragraph).

Therefore, Stone et al. study the effects on the suprapatellar pouch of cynomolgus monkey transplanted with porcine cartilaginous tissue pretreated with α-galactosidase to permanently remove α-gal epitopes from the surface of the tissue. Stone et al. deal with cartilagenous tissue which clearly still exhibits porcine antigens that cause immune attack of the transplanted tissue. There is no teaching relating to the viability of the transplant tissue, no teaching relating to avoiding immune recognition of a transplant to avoid acute rejection, and no suggestion that the transplanted tissue retains the ability to re-express any temporarily removed surface antigens.

In contrast to the teachings of Stone et al., the present invention specifically contemplates the reappearance of temporarily removed surface MHC Class I antigens in order to "re-educate" the host to recognize the donor tissue as "self" tissue:

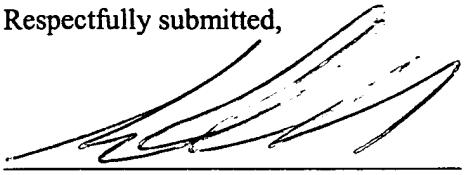
> "Since the tissues will remain viable after treatment according to this invention, expression of MHC molecules will continue, and eventually *reappearance of MHC antigens* on the donor tissue will occur, e.g., after transplantation . . . *Reappearance of MHC antigens* may be used to advantage for inducing tolerance of the donor graft, through *re-education of the recipient's immune system* to recognize and tolerate the donor antigens as they reappear." (See, Specification, page 5, line 32 to page 6, line 8). (emphasis added).

There is no disclosure in Stone et al. that cures the glaring failure of the Oliver et al. patents and the Galati et al. publication to provide any teaching that approximates the method of the invention as defined by the amended claims. Accordingly, reconsideration and withdrawal of the rejection of Claims 10 and 11 under 35 U.S.C. §103 are respectfully requested.

For the reasons set forth above, Applicant respectfully submits that the references cited by the Examiner in the present Office Action, considered together or individually, neither disclose nor suggest the novel method disclosed in the present application for inhibiting rejection of donor tissue transplanted into a recipient mammal.

Entry of the amendments and allowance of the pending claims are respectfully requested.

Respectfully submitted,



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June 23, 2003
date

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